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TITLE: **Radioimmunotherapy (RIT) Dose-Escalation Studies in Prostate Cancer Using Anti-PSMA Antibody ^{177}Lu-J591: RIT Alone and RIT in Combination with Docetaxel,"**

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Two clinical protocols are part of this grant application. In 2007, we started the first Phase I dose escalation study with ^{177}Lu-DOTA-huJ591 mAb using dose fractionation regimen. In patients (n=28)with PCa and recurrent and/or metastatic disease, ^{177}Lu dose (20-45 mCi/m^2/20 mg antibody)was escalated in 6 different dose levels (3-6 pts at each dose level). 22/28 subjects were done under DOD sponsored protocol. Fractionated ^{177}Lu-J591 is well-tolerated, with reversible myelosuppression. MTD with doses is 40 mCi/m^2 (total 80 mCi/m^2). The cumulative dose exceeds the single dose MTD (70 mCi/m^2). PSA declines have been seen despite a potentially sub-optimal (for ^{177}Lu) patient population with bulky metastatic disease. A second phase I study in combination with docetaxel and ^{177}Lu-J591 (20 mCi/m^2; 2 doses) has begun and the first group (n=3) completed. This trial will be completed outside DOD funding. The results of these studies as originally proposed in the grant, clearly demonstrate that the original intent of the SOW have been met and the project can be considered completed. A major reportable outcome is that dose the fractionation of ^{177}Lu-J591 decreases hematological toxicity and appear to result in prolonged PSA declines compared to single higher dose administration. We anticipate that combination therapy may be more efficacious than RIT alone.

15. SUBJECT TERMS
Radioimmunotherapy, Prostate cancer, ^{177}Lu-DOTA-J591 antibody, Dose-Fractionation, Combination therapy

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Introduction

We still lack a systemic treatment that clearly demonstrates improved survival in patients with disseminated hormone resistant prostate cancer (PC). In PC, the most well established, prostate-restricted, cell surface antigen yet identified is prostate specific membrane antigen (PSMA). It is an ideal target for developing therapeutic agents as it is expressed by all the PCs and the expression levels progressively increase in more poorly differentiated, metastatic and hormone-refractory prostate cancers (HRPC). **J591 is a de-immunized monoclonal antibody (mAb) that binds with a very high affinity to the extracellular domain of PSMA on the viable tumor cells.** We have demonstrated radiolabeled J591 sensitively and specifically targets sites of metastatic PC in both bone and soft tissue**.** In a Phase I studies, we have determined that a single dose of ^{177}Lu-J591 (70 mCi/m^2) either decrease or stabilize serum PSA levels. ^{177}Lu has low energy β^- particles and suitable γ photons for dosimetric studies. Therefore **^{177}Lu-J591 may be an ideal agent for RIT studies of PC**. The degree of anti-tumor response following RIT depends on several variables, especially total (cumulative) radiation dose to the tumor, dose-rate and tumor radiosensitivity. Also, myelotoxicity is the dose-limiting factor in RIT. Therefore strategies are needed to optimize dosimetry to the bone marrow and tumor. Dose-fractionation is a practical strategy to decrease the dose to bone marrow while increasing the cumulative radiation dose to the tumor at an optimal dose-rate. Preclinical studies strongly support this strategy. Combined modality radioimmunotherapy (CMRIT) is another strategy designed to enhance the cascade of molecular events required for apoptotic tumor cell death resulting from the continuous low dose-rate radiation. FDA approved anti-neoplastic agent docetaxel can cause microtubular dysfunction and as a result cells are blocked in the G_2/M phase of the cell cycle, thus increasing sensitivity of cells to radiation.

Therefore, **we proposed to perform two independent phase I dose-escalation studies** in patients with HRPC. The first protocol was designed to determine the cumulative MTD of ^{177}Lu-J591, in a fractionated dose regimen of 2 low dose treatments given 2 weeks apart. A second follow up protocol was designed to determine a safe dose of combination therapy (2 doses of ^{177}Lu-J591 + docetaxel (70 mg). This research proposal thus combines several important strategies for successful RIT of PC; a very specific and high affinity anti-PSMA mAb J591, an ideal therapeutic radionuclide ^{177}Lu, dose fractionation to reduce myelotoxicity and finally combination therapy with docetaxel to augment the anti-tumor response of RIT.

Body of Text

Research Accomplishments

Task 1: Preparation of ^{177}Lu-DOTA-J591 mAB for clinical studies

Under GMP conditions, monoclonal antibody HuJ591-GS Antibody was DOTA conjugated, vialed and labeled by Immunomedics Inc (manufacturer of record for the vialed DOTA-HuJ591 antibody drug product). The manufacturer's address and telephone number are:

Immunomedics Inc.
300 Americsn Road
Morris Plains, NJ 07950
Phone: 973-605-8200

The drug product consists of DOTA-HuJ591 antibody in 0.3 M ammonium acetate, pH 7.2, in 2 mL thermoplastic vials with gray butyl rubber stoppers and blue flip-off crimp seal closures. The nominal concentration is 8.0 mg/mL and the nominal fill volume is 1.3 mL. There are no other excipients added.

^{177}Lu-Labeling of DOTA-J591: 3 batches of the above lot of DOTA-J591 were labeled with ^{177}Lu to a specific activity of 10-20 mCi/mg. All the QC tests indicated that the material is suitable for clinical studies.

The above process was started around October 2006 and final tests completed by March 2007.

Task 2: Obtain IRB approval of the Phase I dose escalation protocol using ^{177}Lu-J591 in a fractionated dose regimen

- After 16 months of interaction with HSRRB at DOD, the protocol was finally approved in May 2006. Subsequently, the protocol (modified by Cornell IRB and DOD HSRRB) was submitted to FDA for permission to start the clinical trial under an IND.

- In January 2007, we received the approval from FDA following minor modifications to the protocol as suggested by FDA.

- The protocol was finally approved by Cornell IRB and HSRRB in July 2007 and clinical studies started

Task 3: Phase I clinical trial with ^{177}Lu-J591 Dose fractionation regimen

We started recruitment of patients in this protocol in the fall of 2007 and we have successfully completed the study in the fall of 2010. Important accomplishments of this phase I study are described below:

Methods: In this phase I study, cohorts of 3-6 pts with progressive metastatic CRPC received 2 fractionated doses of ^{177}Lu -J591, 2 weeks apart: Cohort 1 (20 mCi/m^2 x 2), dose escalation 5 mCi/m^2 per dose per cohort up to 45 mCi/m^2 x 2. The primary endpoint was to determine dose limiting toxicity (DLT) and the cumulative maximum tolerated dose (MTD) of fractionated ^{177}Lu -J591 RIT and secondary endpoints of efficacy; ^{177}Lu-J591 scans with semi-quantitative scoring were performed.

Entry Criteria (summary)

- Histologically proven adenocarcinoma of prostate
- Radiographically evident metastatic disease
- Progression despite medical/surgical castration (testosterone < 50)
- Adequate bone marrow and organ function
  (including ANC ≥ 2000, platelet count ≥150)
- ECOG performance status 0-2
- No prior radioisotopes (e.g. strontium, samarium)

Treatment (dose escalation in 6 planned cohorts of 3-6 subjects)

- Cohort 1: initial dose of ^{177}Lu-J591 at 20 mCi/m^2 IV D1, D15
- Each subsequent cohort received escalating doses of 5 mCi/m^2 per dose per cohort (i.e. cumulative dose escalation of 10 mCi/m^2 per cohort)
- No pre-medications given

Definition of Dose Limiting Toxicity (DLT)

- Platelet count < 15,000 > 7 days or need for > 3 plt transfusions in 30 days
- Gr 4 neutropenia > 7 days
- Febrile neutropenia
- Attributable Gr ≥ 3 non-hematologic toxicity (excluding infusion reactions)

Results: A total of 28 pts have been treated, receiving up to 45 mCi/m^2 x2 (highest anticipated dose). The first 22 out of 28 patients were done under DOD sponsored (HSRRB approved) protocol, while the remaining 6 subjects were done only with Cornell IRB approval (only Cornell sponsor).

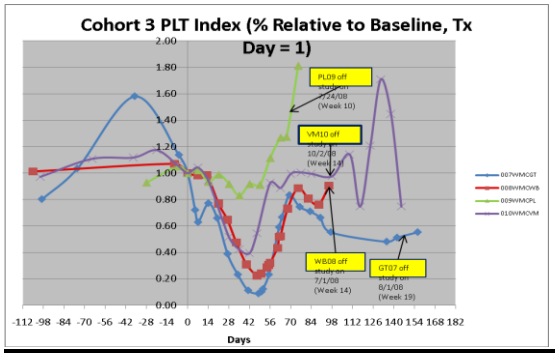
- Median age is 72 (range 57-86),
- Median baseline PSA 49 (2 – 766.5).
- 85% had bone mets and 46% extra-osseous visceral mets (lung, liver). All pts had progressed after 1-4 hormonal therapies and 46% progressed on 1-4 lines of chemotherapy including docetaxel.

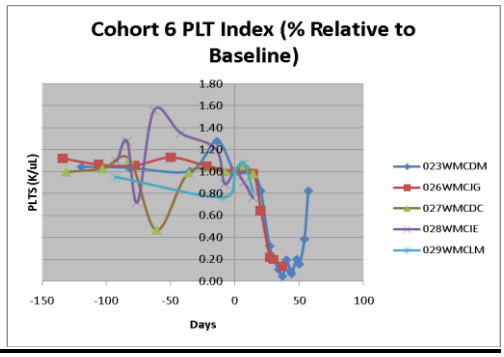
Overall Toxicity (individual subject worst grade, all cohorts)

- Infusion Reactions (without pre-medication)
  10 (36%) overall (9 Gr 1, 1 Gr 3) (All were transient, reversible)
- Thrombocytopenia
  Gr 0 = 18%; Gr 1-2 = 43%; Gr 3 = 18%; Gr 4 = 21%
  No pts had significant bleeding; 2 received plt transfusions (cohort 6)
- Neutropenia
  Gr 0 = 40%; Gr 1-2 = 32%; Gr 3 = 29%; Gr 4 = 11%
  No febrile neutropenia (no growth factor use)
- Transaminitis
  Transient Gr 1 AST 29% (1 Gr 2)
- **Need for** transfusions 6 pts receiving up to 90 mCi/m^2 experienced Gr 4 thrombocytopenia and only 2 (<10% requiring a transfusion). *In contrast, with a **single high dose** of ^{177}Lu-J591 (MTD – 70 mCi/m^2) **40% of patients** require platelet transfusions (shown in a different Phase I study completed in 2005).*

Table-1: Myeolotoxicity following 177Lu-J591 (2 doses, 2 wks apart)

Cohort	Cumulative Dose	Neutrophil		Platelets		AST
		Gr 3	Gr 4	Gr 3	Gr 4	Gr > 0
1 (n=3)	40 mCi/m2	0	0	0	0	1
2 (n=3)	50 mCi/m2	0	0	0	0	0
3 (n=4)	60 mCi/m2	2	0	1	0	0
4 (n=6)	70 mCi/m2	0	0	0	2	3
5 (n=6)	80 mCi/m2	2	2	2	2	3
6 (n=6)	90 mCi/m2	2	2	1	3	2





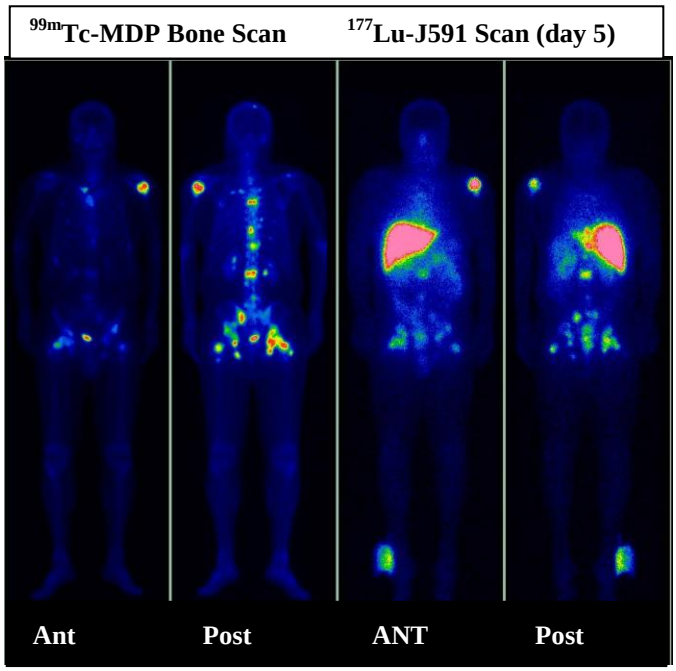
Dose Limiting Toxicity (DLT) and Maximum Tolerated dose (MTD)

- No DLT in Cohorts 1-5
- 2 subjects in Cohort 6 experienced asymptomatic grade 4 neutropenia lasting > 7 days

- **MTD of the regimen is 40 mCi/m^2 x2 (total 80 mCi/m^2)**

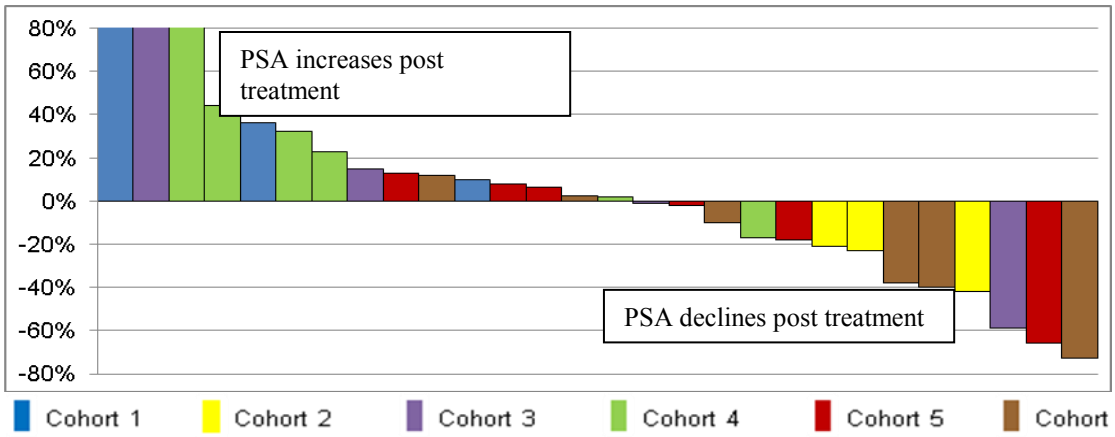
^{177}Lu-J591 PSMA in vivo Targeting Based on Imaging Studies

^{177}Lu-J591 imaging studies demonstrated targeting of known sites of PC metastases when compared to conventional bone scans.



Efficacy Results (PSA Declines)

- Any PSA decline = 46% (all evaluable pts)
- Cohorts 5 & 6 combined: 58% with PSA decline



Task 4: Phase 1 Clinical trial with combination therapy (^{177}Lu-J591 and Docetaxel)

Phase 1 Clinical trial with Combination Therapy (^{177}Lu-J591 and Docetaxel) started and as of July 2009. The goal is to study 5 groups (3 subjects/group) starting with 20 mCi/m^2.

We have enrolled/treated 3 (three) subjects on cohort 1 (dose level 1 = 20 mCi/m^2 x 2). All three subjects completed the study without dose limiting toxicity. The next cohort (dose level =30 mCi/m^2 x 2) opened up in July 2010 and we have enrolled 1 subject so far. We are pre-screening the 2nd subject. The study has recently undergone an amendment changing the definition of DLT and allowing us to expand cohorts prior to dose escalation.

Current Status

The DOD funding officially expired as of September 15, 2010. Application for an extension of NCE was not submitted. The original intent of the SOW-4 has been partially met and we intend to officially consider the project closed for lack of DOD funds. However, we wish to continue recruitment of subjects into the current IRB approved protocol and hope to meet the original intent of SOW-4 without DOD funding and formal approval HRPO. We plan to submit an amendment to current IRB protocol to delete any reference to DOD as a sponsor of the protocol.

Key Research Accomplishments

- Preparation of new lot of DOTA-J591 and optimization of ^{177}Lu labeling.

- Successfully completed Phase I dose-escalation and fractionated dose regimen clinical trial in 28 patients with prostate cancer.

- We have determined that the MTD with dose fractionation (2 doses, 2 weeks apart) of ^{177}Lu-J591 mAb is 80 mCi/m^2. In comparison the MTD for a single high dose of ^{177}Lu-J591 is 70 mCi/m^2.

- We also demonstrated that patients tolerated dose fractionation regimen better than a single high dose and the number of subjects needing platelet transfusion was <10%. In comparison, with a single high dose ^{177}Lu-J591, 40% of patents needed platelet transfusion.

- We have started Phase 1 clinical trial with combination therapy (^{177}Lu-J591 and Docetaxel) started. Completed the first cohort of 3 subjects without any significant myelotoxicity.

REPORTABLE OUTCOMES

1. The results of the Phase I study were presented at the 2010 annual scientific meeting of the American Society of Clinical Oncologists in Chicago, IL.

   Abstract #51006

   Phase I trial of fractionated-dose 177lutetium radiolabeled anti-prostate-specific membrane antigen (PSMA) monoclonal antibody J591 (177Lu-J591) in patients (pts) with metastatic castration-resistant prostate cancer (metCRPC).

   S. T. Tagawa, S. Vallabhajosula, J. Osborne, S. J. Goldsmith, K. Petrillo, L. Tyrell, G. S. Dhillon, H. Beltran, N. H. Bander, D. M. Nanus; Weill Cornell Medical College, New York, NY

2. The results of Phase I studies with dose fractionation and combination therapy will be presented at the 2011 IMPaCT conference sponsored by the Department of Defense (DOD) Prostate Cancer Research Program (PCRP) in March 2011.

   PC040566-1890

   LU-177 LABELED ANTI-PSMA MONOCLONAL ANTIBODY J591: PHASE I TRIAL OF DOSE FRACTIONATION AND COMBINATION THERAPY WITH DOCETAXEL IN PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER

   Shankar Vallabhajosula, Scott T. Tagawa, Anastasia Nikolopoulou, Joseph R. Osborne, Stanley J. Goldsmith, David M. Nanus, and Neil H. Bander, Cornell University, Weill Cornell Medical College

CONCLUSION

Fractionated dose ^{177}Lu-J591 is well tolerated, with reversible myelosuppression. With dose-fractionation, patients are able to tolerate higher cumulative doses than with single-dose ^{177}Lu-J591 (confirming our hypothesis) and some efficacy has been demonstrated. Building upon these data, a phase I fractionated-dose ^{177}Lu-J591 plus docetaxel study has begun enrollment, utilizing improved tolerability of fractionated dose RIT plus the radiosensitizing and debulking properties of docetaxel.

REFFERENCES

1. Smith-Jones PM**.** Vallabhajosula S, Bastidas D, Hunter C, Navarro V, Bander NH and Goldsmith SJ. Preclinical studies with 131I and 111In labeled monoclonal antibodies, specific for either the intracellular or extracellular domains of prostate specific membrane antigen. J Label Comp Radioph 1999; 42:suppl 1,s701-703

2. Smith-Jones PM, Vallabhajosula S, Goldsmith SJ, Navarro V, Hunter CJ, Bastidas D, Bander NH. In vitro Characterization of Radiolabeled Monoclonal Antibodies Specific for the Extracellular Domain of Prostate-specific Membrane Antigen. Cancer Res 2000; 60:5237-5243.

3. Smith-Jones PM, Vallabhajosula S, St. Omer S, Navarro V, Goldsmith SJ, Bander NH, 177Lu-DOTA-HuJ591: A new Radiolabeled monoclonal antibody (MAb) for targeted therapy of prostate cancer. J Label Compds Radiopharm 2001;44:Suppl 1:90-92.

4. Smith-Jones PM, Vallabhajosula S, Navarro V, et al: Radiolabeled monoclonal antibodies specific to the extracellular domain of prostate-specific membrane antigen: preclinical studies in nude mice bearing LNCaP human prostate tumor. J Nucl Med 44:610-7, 2003

5. Nanus D, Milowsky MI, Kostakoglu L, Smith-Jones PM, Vallabahajosula S, Goldsmith SJ and Bander NH: Clinical use of Monoclonal Antibody HuJ591 Therapy: Targeting Prostate Specific Membrane Antigen. *J Urol*, 2003:**170**:S84-S89.

6. Bander, NH, Trabulsi E, Kostakoglu L, Yao D, Vallabhajosula S, Smith-Jones P, Joyce MA, Milowsky M, Nanus DM and Goldsmith SJ: Targeting Metastatic Prostate Cancer with Radiolabeled Monoclonal Antibody J591 in the Extracellular Domain of Prostate Specific Membrane Antigen. *J Urol*,2003;**170**:1717-1721.

7. Bander, N.H., Nanus, D.M., Milowsky, M.I., Kostakoglu, L., Vallabahajosula, S., and Goldsmith, S.J.: Targeted systemic therapy of prostate cancer with a monoclonal antibody to prostate specific membrane antigen (PSMA). *Seminars in Oncology*,2003;**30**:667-677.

8. Vallabhajosula S, Kothari PA, Konishi S, Hamacher KA, Goldsmith SJ, Bander NH. Radiolabeled J591 antibody specific to prostate specific membrane antigen (PSMA): comparison of Indium-111, Yttrium-90 and Lutetium-177. J Label Radiopharma Compunds 2003;

9. Vallabahajosula S, Smith-Jones PM, Navarro V, Goldsmith SJ and Bander NH: Radioimmunotherapy Of Prostate Cancer In Human Xenografts Using Monoclonal Antibodies Specific To Prostate Specific Membrane Antigen (PSMA): Studies In Nude Mice. The Prostate 2004;58:145-155.

10. Milowsky MI, Nanus DM, Kostakoglu L, **Vallabhajosula S**, Goldsmith SJ, Bander NH. Phase I Trial of ^{90}Y-Labeled Anti-PSMA Monoclonal Antibody J591 For Androgen-Independent Prostate Cancer. J Clin Oncol 2004; **J Clin Oncol** 2004;22:2522-2531

11. Konishi S, Hamacher KA, Vallabhajosula S, Kothari P, Bastidas D, Bander NH, Goldsmith SJ. Determination of Immunoreactive Fraction of Radiolabeled MAbs: What is an Appropriate Method? Cancer Biother and Radiopharmma 2004;19:706-715

12. Vallabhajosula S; Kuji I; Hamacher KA; Konishi S; Kostakoglu L; Kothari PA; Milowski MI; Nanus DM; Bander NH; Goldsmith SJ. Pharmacokinetics and biodistribution of ^{111}In- and ^{177}Lu-labeled J591 antibody specific for prostate-specific membrane antigen: prediction of ^{90}Y-J591 radiation dosimetry based on ^{111}In or ^{177}Lu? J Nucl Med 2005;46:634-641

13. Vallabhajosula S; Goldsmith SJ; Hamacher KA; Kostakoglu L; Konishi S; Milowski MI; Nanus DM; Bander NH. Prediction of myelotoxicity based on bone marrow radiation-absorbed dose: radioimmunotherapy studies using ^{90}Y- and ^{177}Lu-labeled J591 antibodies specific for prostate-specific membrane antigen. J Nucl Med 2005;46: 850-858

14. Bander NH; Milowsky MI; Nanus DM; Kostakoglu L; Vallabhajosula S; Goldsmith SJ Phase I Trial of ^{177}Lutetium-Labeled J591, a Monoclonal Antibody to Prostate-Specific Membrane Antigen, in Patients With Androgen-Independent Prostate Cancer. J Clin Oncol 2005;20;23(21): 4591-4601

15. David KA, Milowsky MI, Kostakoglu L, Vallabhajosula S, Goldsmith SJ, Nanus DM, Bander NH**.** Clinical utility of radiolabeled monoclonal antibodies in prostate cancer. Clinical Genitourinary Cancer*. 4:249-56, 2006*

16. Milowsky MI, Nanus DM, Kostakoglu L, Sheehan CE, Vallabhajosula S, Goldsmith SJ, Ross JS, and Bander NH. Vascular Targeted Therapy With Anti–Prostate-Specific Membrane Antigen Monoclonal Antibody J591 in Advanced Solid Tumors. J Clin Oncol 2007; 25:540-547.